REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration, because the amendments amplify issues previously discussed throughout prosecution; does not raise additional search burden; and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented, because it is made in response to arguments raised in the final rejection. Entry of the Amendment, reexamination, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

1. Status of the Claims

The status of the claims following entry of the amendments is as follows:

Claims canceled: 1-48, 50, 57-58, and 63-66

Claims pending: 49, 51-56, 59-62, and 67-68

Claims rejected: 36-68

Claims objected: 59-60

Claims amended: 49, 51, 55, 59-62, and 67

2. Support for Amendments

Claim 49 is amended to incorporate elements from claims 50 and 63-65 (now canceled). Claims 51, 55, 59-62, and 67 are amended to more precisely recite the claimed subject matter. Support for the claims amendments can be found at least from the claims previously presented. Applicants do not believe that the amendments add prohibited subject matter that is unsupported by the Specification as filed.

The claims have been amended without prejudice to, or disclaimer of, the canceled subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter canceled by way of amendments.

3. Acknowledgement of Information Disclosure Statements

Applicants appreciate the Office's acknowledgement of the Information Disclosure Statement (IDS) filed August 3, 2010.

The Office is respectfully requested to acknowledge the Search Report (dated December 13, 2004) listed on the IDS submitted November 15, 2007. The Search Report was submitted to the Office on March 28, 2006, when the national application was filed. Accordingly, Applicants respectfully request that the Office returns the initialed PTO-1449 form with the Office's next communication.

4. Withdrawn Objections and Rejections

Rejections and objections not reiterated are withdrawn. *See* 37 C.F.R. § 1.113(b); M.P.E.P. §§ 706.07 and 707.07(e).

5. Claim Objections

The Office objects to claim 59-60, suggesting that (1) the phrase "P10 and P3 positions" in claim 59 should be corrected to "***the*** P10 and P3 positions," and (2) the phrase "P5 and P3 positions" in claim 60 should be corrected to "***the*** P5 and P3 positions."

Applicants appreciate the Office's suggestions and amend claims 59-60 accordingly. Applicants respectfully request withdrawal of the objection and allowance of the claims.

6. Rejection under 35 U.S.C. § 101

The Office rejects claims 36-68 under 35 U.S.C. § 101 as allegedly failing to set forth any step involved in the process. Office Action, pages 2-3.

Applicants traverse the rejection to the extent it may be applied to the amended claims. As amended, claim 49 recites *inter alia* a process comprising "***cleaving***" a polypeptide. Amended claim 49, as well as its dependent claims 51-56, 59-62, and 67-68, thus sets forth at least one active step—"cleaving." Claims 36-48, 50, 57-58, and 63-66 are canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

7. Rejection under 35 U.S.C. § 112, Second Paragraph

7.1. Claims 36-68

The Office rejects claims 36-68 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, page 4. The Office alleges that the claims fail to set forth any active, positive step involved in the claimed process. *Id.*

Applicants traverse the rejection to the extent it may be applied to the amended claims. As amended, claim 49 recites *inter alia* a process comprising "***cleaving***" a polypeptide. Amended claim 49, as well as its dependent claims 51-56, 59-62, and 67-68, thus sets forth at least one active step—"cleaving." Claims 36-48, 50, 57-58, and 63-66 are canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

7.2. Claims 36, 51, 55, 59-60, and dependent claims

The Office rejects claims 36, 51, 55, 59-60, and dependent claims under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, page 4.

Claim 36 is canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claims.

Claims 51 and 55 allegedly lack antecedent basis for reciting "the sequence." *Id.* The Office also alleges that the recited "a P10 position" and "a P3 position" should be corrected to "the P10 position" and "the P3 position." *Id.* Applicants traverse the rejection to the extent it may be applied to the amended claims. Applicants note that there is sufficient antecedent basis for reciting "the sequence" in claims 51 and 55, because the recited "polypeptide" and "cleavage site" inherently would have referred to the sequence. *See e.g., Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359, 61 U.S.P.Q.2d 1216, 1218-19 (Fed. Cir. 2001) (holding that inherent components of elements recited have antecedent basis in the recitation of the components themselves); *see also* M.P.E.P. § 2173.05(e). On the other side, Applicants believe that claims 51 and 55 correctly recite "a P10 position" and "a P3 position" when these positions are first recited. Applicants respectfully request withdrawal of the rejection and allowance of claims.

The Office suggests that claim 55 should recite "process" instead of "method." Office

Action, page 5. As amended, claim 55 recites "process." Applicants respectfully request withdrawal of the rejection and allowance of claim 55.

The Office assumes that "is composed of" as recited in claim 67 means "consists of." *Id.* As amended, claim 67 recites "consists of." Applicants respectfully request withdrawal of the rejection and allowance of claim 67.

8. Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

8.1. Claims 36-47 and 66

The Office rejects claims 36-47 and 66 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Office Action, page 6. Upon entry of the present amendments, claims 36-47 and 66 are canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection.

8.2. Claims 48-65 and 67-68

The Office rejects claims 48-65 and 67-68 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Office Action, page 11. The Office alleges that the claims are "not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims." *Id.*, at 15. For example, the Office alleges that (1) the genus of the cleavage motifs encompasses more than 8.2×10^{17} arrays; and (2) the specification does not support the broad scope of claims 48-65 and 67-68. *Id.* The Office further discounts Applicants' arguments in the prior response by stating the following:

> Importantly, as explained in the prior action, the results of Kramer et al, showing only 6% activity for cleavage between Arg↓Arg disagrees with Applicants' results showing that ***the D97A OmpT variant had 70% of the activity of the parent protease for Arg↓Arg (Table 1)***. Thus, as also explained in the prior action, cleavage by the recited OmpT protease variants remained unpredictable and the specification provides little evidence as to which amino acid residues are favored, permitted, or non-favored at positions P10-P2 and P2-P5', for cleavage by the $D^{97}A$ variant and the other recited variants..

Id., at 19 (emphasis added).

Applicants traverse the rejection to the extent it may be applied to the amended claims. First, the Office must provide objective evidence or reasoning that the skilled artisan would doubt the enablement provided by the specification. *See In re Cortright*, 165 F.3d 1353, 1357, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). Further, whether undue experimentation is required to practice an invention is determined by the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 736, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Applicants' traversal is at least on the following grounds. First, the Office fails to provide objective evidence or reasoning that the skilled artisan would have doubted the enablement provided by the specification. *See, e.g., Cortright*, 165 F.3d at 1357, 49 U.S.P.Q.2d at 1466. Applicants believe that the Office mischaracterizes the present application. There is no support for the Office's assertion that "the D97A OmpT variant had ***70%*** of the activity of the parent protease of Arg↓Arg (Table 1)." Applicants respectfully direct the Office to Table 1 of the present application:

TABLE 1

Cleavage of fusion proteins PRX with OmpT protease variants OmpT D97X

Fusion proteins	OmpT protease variants OmpT D97X											
PRX	D97D	D97A	D97L	D97F	D97M	D97S	D97T	D97C	D97N	D97Q	D97E	D97H
PRA	5.4	3.8	7.1	3.1	6.0	4.0	6.8	6.2	3.8	4.0	6.5	8.4
PRV	3.5	—	—	—	3.0	—	—	3.2	—	—	5.0	7.8
PRI	—	—	—	—	—	—	—	—	—	—	—	3.1
PRF	—	—	4.7	—	7.7	—	3.7	4.6	—	—	3.4	4.1
PRM	—	—	—	—	—	—	—	—	—	—	—	4.6
PRS	3.9	—	9.1	—	7.1	—	7.4	5.6	4.1	4.4	7.2	8.7
PRT	—	—	—	—	—	—	—	—	—	—	—	3.0
PRC	3.1	—	3.9	—	6.5	3.1	4.6	4.8	—	4.1	6.9	11
PRY	—	—	3.2	—	6.2	—	—	—	—	—	—	—
PRN	—	—	—	—	—	—	—	—	—	—	—	3.5
PRK	88	—	—	—	—	—	—	3.9	—	—	39	4.5
PRR	100	—	—	—	—	—	—	4.0	—	—	49	4.6

The above blocked section of Table 1 actually indicates that the OmpT D97A variant cleaves PRR (Arg↓Arg as shown in FIG. 1) at a low efficiency (less than 3.0% of the efficiency for reaction between wild-type OmpT and PRR). As the present application employs a different substrate than the one in Kramer, Applicants do not believe there is any disagreement or inconsistency between Kramer's results and what is disclosed in the Specification. Applicants can not locate the alleged "***70%***" efficiency that is relied upon by the Office. Accordingly, the Office's allegation as to unpredictability is unsupported.

Second, the Specification provides multiple working examples wherein various OmpT 97th amino acid variants cleave numerous motifs within the scope of the claims. The degree of exemplification reasonably correlated with the scope of the claims. Applicants note that even in an unpredictable art, exemplification of each and every embodiment encompassed by a claim is not required to comply with the enablement requirement. *See e.g., In re Angstadt*, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Third, the Office has not provided any objective evidence or reasoning why the presently claimed processes are not enabled or even provided examples or a rationale of why the claimed processes would not work. Applicants submit that "it is incumbent upon the Patent Office ... to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Given at least these arguments, the Office has failed to adduce a *prima facie* argument for lack of enablement. Claims 48, 50, 57-58, and 63-65 are canceled, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

9. Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

The Office rejects claims 36-47, 50-58, 60-63, 65 and 67-68 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description

requirement. Office Action, page 19. The Office discounts Applicants' arguments in the prior response by stating the following:

> However, in the instant case, out of $3.6 \times 10^{15} - 3.3 \times 10^{18}$ encompassed methods for each E. coli protein variant, the specification has described only a few, or no, functional permutations. Thus the methods are not described such that the skilled artisan would recognize possession.

Id., at 28-29.

Applicants traverse the rejection to the extent it may be applied to the amended claims. Whether generic claims to biological subject matter comply with the written description requirement is determined by an analysis of the *Capon* factors: (1) the existing knowledge in the particular field, (2) the extent and content of the prior art, (3) the maturity of the science or technology, (4) the predictability of the subject matter at issue, and (5) other considerations appropriate to the subject matter. *See Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005); *see also Ariad Pharmaceuticals Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351, 94 U.S.P.Q.2d 1161, 1172 (Fed. Cir. 2010) (*en banc*) (citing *Capon* with approval). In the present rejection, the Office has failed to perform an analysis of the above factors. Thus, no *prima facie* argument for lack of written description has been adduced.

Furthermore, the Federal Circuit explicitly holds that working examples covering the full scope of the claims are not required for an adequate written description. *See e.g., Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006);[1] *see also Ariad* at 598 F.3d 1336, 1352, 94 U.S.P.Q.2d at 1172.[2] Accordingly, the Office's assertion as to inadequacy of working examples ("functional permutations") is unsupported. The Specification provides multiple working examples, wherein OmpT cleaves numerous motifs within the scope of the claims. *See, e.g.*, Specification, Examples 2, 4, 6, 8, 10, and 17-18.

Given at least these arguments, amended claims comply with the written description requirement. Claims 36-47, 50, 57-58, 63, and 65 are canceled, mooting the rejection.

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1 "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before."

Accordingly, Applicant respectfully requests withdrawal of the rejection and allowance of the claims.

10. Rejections under 35 U.S.C. § 102(b)

The Office rejects claims 36 and 44 under 35 U.S.C. § 102(b) as allegedly anticipated by **Sugimura 1988a** as evidenced by either **Okuno 2002b** or **Dekker** (*see* enclosed **EXHIBIT I** for abbreviations used for cited references). Office Action, page 29. The Office also rejects claims 36 and 43-45 under 35 U.S.C. § 102(b) as allegedly anticipated by **Stumpe**. *Id.*

Upon entry of the present amendments, claims 36 and 43-45 are canceled, mooting the rejection. Applicants respectfully request withdrawal of the rejection.

11. Rejections under 35 U.S.C. § 103(a)

11.1. Claims 36-48, 50, 57-58, and 63-66

Upon entry of the present amendments, claims 36-48, 50, 57-58, and 63-66 are canceled, mooting at least the following § 103(a) rejections:

(1) claims 36 and 43-46 over **Stumpe** in view of **Suzuki** and **Kramer** (Office Action, page 30);

(2) claims 36-40 over the combination of **Stumpe**, **Suzuki**, and **Kramer** in view of **Yamamoto** and **Dekker** (Office Action, page 31);

(3) claim 41 over the combination of **Stumpe**, **Suzuki**, **Kramer**, **Yamamoto**, and **Dekker**, in view of **Yabuta** (Office Action, page 33);

(4) claims 42 and 66 over the combination of **Stumpe**, **Suzuki**, and **Kramer** in view of **Dekker** and **Okuno 2002b** (Office Action, page 34);

(5) claim 48 over the combination of **Stumpe**, **Suzuki**, and **Kramer**, in view of **Metzler** (Office Action, page 35);

(6) claims 57-58 over the combination of **Stumpe**, **Suzuki**, **Kramer**, **Yamamoto**, **Dekker**, and **Metzler** in view of **Dekker** and **Okuno 2002b** (Office Action, page 38);

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[2] "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement."

(7) claims 50 and 63-65 over **Okuno 2002a** and **Dekker**, in view of **Kramer** (Office Action, page 39);

(8) claims 50 and 63-64 over the combination of **Okuno 2002a**, **Dekker**, and **Kramer**, in view of **Metzler** (Office Action, page 41); and

(9) claims 50 and 65 over the combination of **Okuno 2002a**, **Dekker**, and **Kramer**, in view of **Metzler** (Office Action, page 43).

Accordingly, Applicants respectfully request withdrawal of the above rejections.

11.2. Claim 49

The Office rejects claim 49 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of **Sugimura 1988a**, **Okuno 2002a**, **Okuno 2002b**, **Dekker**, and **Kramer**, in view **Metzler**. Office Action, page 36. The Office admits that Sugimura 1988a, Okuno 2002a, Okuno 2002b, and Dekker do not teach cleaving with an OmpT protease 97th amino acid variant. *Id.* Kramer allegedly teaches that an OmpT protease D97A variant cleaves at Ala-Arg↓Arg-Ala. *Id.* The Office then concludes that it would have been obvious for a skilled artisan to use the OmpT D97A variant to cleave the proteins of Sugimura 1988a, Okuno 2002a, Okuno 200b, and Dekker, because (1) there is motivation to combine the references; and (2) the expectation of success is high. *Id.*, at 36-37.

Applicants traverse the rejection to the extent it may be applied to the amended claim. To render a claim obvious, both the suggestion of the claimed invention and the expectation of success must be in the prior art, not from the disclosure of the claimed invention. *In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Additionally, "obviousness requires a suggestion of ***all*** limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 U.S.P.Q.2d 1940, 1947 (Fed. Cir. 2003) (emphasis added). The Office must also establish that one of ordinary skill in the art would have had a reasonable expectation of success to practice the claimed invention. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

As amended, claim 49 recites *inter alia* cleaving a polypeptide with an *E. coli* OmpT protease 97th amino acid variant, wherein the variants and the cleavage sites are arranged according to the following table:

	The 97th Amino Acid of the Variant	Cleavage Site	
		P1	P1'
I	Leucine (D97L)	Arginine or Lysine	Serine or Alanine
II	Methionine (D97M)	Arginine or Lysine	Phenylalanine, Alanine, Serine, Cysteine, or Tyrosine
III	Histidine (D97H)	Arginine or Lysine	Alanine, Valine, Isoleucine, Methionine, Serine, Threonine, Cysteine, or Asparagine

Kramer teaches cleavage of a substrate by an OmpT D97A variant, wherein the substrate is Abz-Ala-Arg↓Arg-Ala-Dap(dnp)-Gly. *See* Kramer, "*2.1 Materials*," left col., page 427. Applicants submit that Kramer does not teach any of the recited *E. coli* OmpT protease 97th amino acid variants (*i.e.*, D97L, D97M, and D97H). Thus, the combination of Sugimura 1988a, Okuno 2002a, Okuno 2002b, Dekker, and Kramer fails to teach at least the recited *E. coli* OmpT protease 97th amino acid variants. Without all claim elements taught, there can be no expectation that the presently claimed methods would have worked predictably.

Furthermore, the OmpT D97A variant cleaved the Abz-Ala-Arg↓Arg-Ala-Dap(dnp)-Gly substrate with only 6% efficiency, relative to the wild-type OmpT. The Office has not explained, however, why the skilled artisan, knowing that an OmpT D97A variant shows only 6% of the wild-type activity, would have been directed to make additional variants (*e.g.*, OmpT D97L, D97M, and/or D97H) to cleave any of the substrates taught in Sugimura 1988a, Okuno 2002a, Okuno 2002b, and Dekker. Applicants submit that Kramer actually teaches away from making 97th amino acid variants, because Kramer's only attempt to make such a variant produces poor results. Additionally, there is no evidence on the record that a skilled artisan, from all the taught substrates, would have been directed to select only those presently recited, let alone that the cleavage would have been worked predictably. Accordingly, the Office's position is

unsupported by insisting that the artisan would have been motivated to combine the references by the general desire to cleave substrates with OmpT.

The only way the Office appears to achieve combining the elements from the references is through impermissible hindsight reasoning guided by Applicants' own specification. Applicants submit that the Office is not permitted in an obviousness analysis to "pick and choose among individual parts of assorted prior art references as a mosaic to recreate a facsimile of the claimed invention." *See AKZO N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1781, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

Given at least these arguments, amended claim 49 is nonobvious over the cited references. Applicants respectfully request withdrawal of the rejection and allowance of claim 49.

11.3. Claims 51-56, 59-61, and 67-68

The Office rejects claims 51-56, 59-61, and 67-68 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of **Stumpe, Suzuki, Kramer, Yamamoto**, and **Dekker**, in view of **Metzler**. Office Action, page 37. The combination of Stumpe, Suzuki, Kramer, Yamamoto, and Dekker allegedly teaches cleaving RRRAR↓FVPIFTYGELQRMQEKERNKGQ, wherein an amino acid other than arginine or lysine is located at the P1' position. *Id.*, at 37-38. The Office admits that the above combination does not teach using an OmpT 97th amino acid variant. *Id.*, at 38. The Office relies upon Metzler and Kramer to assert that a skilled artisan would have been directed to use an OmpT D97E variant to cleave RRRAR↓FVPIFTYGELQRMQEKERNKGQ. *Id.*

Applicants traverse. Claims 51-56, 59-61, and 67-68 depend directly or indirectly from claim 49. Claim 49 as amended recites *inter alia* cleaving a polypeptide with an *E. coli* OmpT protease 97th amino acid variant, D97L, D97M, or D97H. *See* table in Section 11.2 *supra*. Kramer does not teach any of the recited *E. coli* OmpT D97L, D97M, and D97H. Metzler is relied upon for its alleged teachings as to the classification of amino acids based on charge, hydrophobicity, and size. Metzler does not teach OmpT variants. Applicants submit that the combination of Kramer and Metzler does not teach any of the recited *E. coli* OmpT protease 97th

amino acid variants (*i.e.*, D97L, D97M, and D97H). Thus, the combination of Stumpe, Suzuki, Kramer, Yamamoto, and Dekker, in view of Metzler fails to teach at least the recited *E. coli* OmpT protease 97th amino acid variants. Without all claim elements taught, there can be no expectation that the presently claimed methods would have worked predictably.

Furthermore, the OmpT D97A variant of Kramer cleaved the Abz-Ala-Arg↓Arg-Ala-Dap(dnp)-Gly substrate with only 6% efficiency, relative to the wild-type OmpT. The Office has not explained, however, why the skilled artisan, knowing that an OmpT D97A variant shows only 6% of the wild-type activity, would have been directed to make additional variants (*e.g.*, OmpT D97L, D97M, and/or D97H) to cleave any of the substrates taught in Stumpe, Suzuki, Kramer, Yamamoto, and Dekker. Applicants submit that Kramer actually teaches away from making 97th amino acid variants, because Kramer's only attempt to make such a variant produces poor results. Additionally, there is no evidence on the record that a skilled artisan would have been directed to select from all the taught substrates only those presently recited, let alone that the cleavage would have been worked predictably. The only way the Office appears to achieve combining the elements from the references is through impermissible hindsight reasoning guided by Applicants' own specification.

Given at least these arguments, claims 51-56, 59-61, and 67-68 are nonobvious over cited references. Applicants respectfully request withdrawal of the rejection and allowance of claims.

11.4. Claims 49 and 54-56

The Office rejects claims 49 and 54-56 under 35 U.S.C. § 103(a) as allegedly unpatentable over **Okuno 2002a** and **Dekker**, in view of **Kramer**. Office Action, page 39. Okuno 2002a and Dekker allegedly teach OmpT cleavage sites having an amino acid other than arginine or lysine at the P1' position. *Id.*, at 39-40. The Office admits that Okuno 2002a and Dekker do not teach cleaving the said protein sequences with any OmpT 97th amino acid variant. *Id.*, at 40. Kramer's allegedly teachings are as discussed above. The Office then concludes that it would have been obvious for a skilled artisan to use the OmpT D97A variant to cleave the proteins of Okuno 2002a, Okuno 200b, and Dekker, because (1) there is motivation to combine the references; and (2) the expectation of success is high. *Id.*

Applicants traverse the rejection to the extent it may be applied to the amended claims. Claim 49 as amended recites *inter alia* cleaving a polypeptide with an *E. coli* OmpT protease 97th amino acid variant, D97L, D97M, or D97H. *See* table in Section 11.2 *supra*. . As discussed in Section 11.2 *supra*, Kramer does not teach any of the recited *E. coli* OmpT protease 97th amino acid variants (*i.e.*, D97L, D97M, and D97H). Thus, the combination of Okuno 2002a, Dekker, and Kramer fails to teach at least the recited *E. coli* OmpT protease 97th amino acid variants. Without all claim elements taught, there can be no expectation that the presently claimed methods would have worked predictably.

Furthermore, the OmpT D97A variant cleaved the Abz-Ala-Arg↓Arg-Ala-Dap(dnp)-Gly substrate with only 6% efficiency, relative to the wild-type OmpT. The Office has not explained, however, why the skilled artisan, knowing that an OmpT D97A variant shows only 6% of the wild-type activity, would have been directed to make additional variants (*e.g.*, OmpT D97L, D97M, and/or D97H) to cleave any of the substrates taught in Okuno 2002a and Dekker. Applicants submit that Kramer actually teaches away from making 97th amino acid variants, because Kramer's only attempt to make such a variant produces poor results. Additionally, there is no evidence on the record that a skilled artisan, from all the taught substrates, would have been directed to select only those presently recited, let alone that the cleavage would have been worked predictably. The only way the Office appears to achieve combining the elements from the references is through impermissible hindsight reasoning guided by Applicants' own specification.

Given at least these arguments, claim 49 is nonobvious over cited references. Dependent claims 54-56 are likewise nonobvious for at least the same reasons. Applicants respectfully request withdrawal of the rejection and allowance of claims.

11.5. Claims 49 and 51

The Office rejects claims 49 and 51 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of **Okuno 2002a**, **Dekker**, and **Kramer**, in view of **Metzler**. Office Action, page 41. The Office alleges that the combination of Okuno 2002a, Dekker, and Kramer renders it obvious to apply the OmpT protease D97A variant of Kramer to cleave one or more

substrates having amino acids other than Arg or Lys at the P1' position. *Id.* The Office admits that the combination of Okuno 2002a, Dekker, and Kramer does not teach OmpT 97th amino acid variants other than OmpT D97A. *Id.* Relying on Metzler's purported teachings as to the classification of amino acids based on charge, hydrophobicity, and size, the Office alleges that a skilled artisan would have believed:

> (i) the OmpT protease variants having a substitution at Asp^{97} with any of Ala, Leu, Phe, and Met would cleave a substrate comprising a P1' of I, F, V, A, Y, M, W, or L and (ii) the OmpT protease variants having a substitution at Asp^{97} with any of Ser, Thr, Cys, Asn, and Gln would cleave a substrate comprising a P1' of S, C, N, Q, T, or G.

Id., at 42. The Office further asserts that (1) neutral/hydrophobic amino acids are more likely to associate with each other; (2) small hydrophobic/polar amino acids are more likely to associate with each other; and (3) substrate binding and cleavage is coordinated by the residues Glu^{27}, Asp^{83}, Asp^{85}, Asp^{208}, Asp^{210}, and His^{212} of the OmpT protease. *Id.*

Applicants traverse the rejection to the extent it may be applied to the amended claims. Claim 49 as amended recites *inter alia* cleaving a polypeptide with an *E. coli* OmpT protease 97th amino acid variant, D97L, D97M, or D97H. *See* table in Section 11.2 *supra*. The Office admits that the combination of Okuno 2002a, Dekker, and Kramer does not suggest making and/or using any OmpT protease variants other than D97A. Metzler is relied upon for its purported teachings as to the classification of amino acids based on charge, hydrophobicity, and size. Metzler does not teach OmpT variants. Thus, Metzler does not cure the defects of the combined Okuno 2002a, Dekker, and Kramer. Applicants submit that the cited references fail to teach at least the claimed OmpT variants. Without all claim elements taught, there can be no expectation that the claimed methods would have worked predictably.

Even if it were assumed *arguendo* that a skilled artisan given Metzler's teachings were directed to make and/or use other OmpT protease variants other than OmpT D97A, the skilled artisan would not have had a reasonable expectation of success making and/or using the OmpT variants as presently claimed. First, Kramer's OmpT D97A variant cleaved the Abz-Ala-Arg↓Arg-Ala-Dap(dnp)-Gly substrate with only 6% efficiency, relative to the wild-type OmpT. The Office has not explained why the skilled artisan, knowing that an OmpT D97A variant

shows only 6% of the wild-type activity, would have been directed to make additional variants to cleave any of the substrates taught in Okuno 2002a and Dekker. Applicants submit that Kramer actually teaches away from making 97th amino acid variants, because Kramer's only attempt to make such a variant produces poor results.

Second, there is no evidence on the record that a skilled artisan, even if directed to make OmpT 97th amino acid variants, would have been directed to select D97L, D97M, and D97H among other substitutions.

Third, there is no evidence on the record that a skilled artisan, from all the taught substrates, would have been directed to select only those presently recited, let alone that the cleavage by the recited OmpT variants would have worked predictably.

Finally, the Office's assertion as to substrate binding and cleavage coordination is unsupported. According to Fig.4 of Kramer, multiple Asp residues (*e.g.*, Asp^{83}, Asp^{85}, Asp^{208}, Asp^{210}) are also involved in the formation of OmpT protease's active site and thus required for substrate binding and cleavage coordination. The Office fails to provide a rationale why a skilled artisan would have been directed to instead substitute the Asp residue at the 97th position among other Asp residues.

In summary, there would be no expectation that the presently claimed process would have worked predictably. Applicants submit that the only way the Office appears to achieve combining the elements from the references is through impermissible hindsight reasoning guided by Applicants' own Specification.

Even if the Office's reliance on and interpretation of Metzler were proper (Applicants do not necessarily agree upon), the claimed methods offer unexpected results. Applicants respectfully direct the Office to Table 1, at page 46 of the Specification. The claimed OmpT D97L variant (Asp97 is substituted by leucine) cleaves PRS (serine at the P'1 position) at a higher efficiency than PRA (alanine at the P'1 position). Similarly, Table 1 of the Specification indicates that the claimed OmpT D97M variant (Asp97 is substituted by methionine) cleaves PRS at a higher efficiency than PRA. Both of these observations are contrary to the Office's interpretation of Metzler, which would have concluded that OmpT D97L or OmpT D97M would have a higher cleavage activity toward a substrate having I, F, V,

A, Y, M, W, or L at the P'1 position ("neutral/hydrophobic amino acids are more likely to associate with each other").

Applicants further note that the results observed for the claimed OmpT D97H variant (Asp97 is substituted by histidine) are also unexpected in view of the cited references. Based on Fig. 4 of Kramer, a skilled artisan may have expected that an OmpT variant having a basic amino acid at the 97th position would have had a high cleavage specificity toward a substrate having an acidic amino acid at the P'1 position. However, the present inventors have found that OmpT D97H variant (histidine is a typical basic amino acid according to Metzler) hardly cleaved substrates having an acidic amino acid at the P'1 position. *See* Example 13 and first paragraph at page 47 of the Specification. Instead, OmpT D97H effectively cleaves substrates having a neutral amino acid (*e.g.*, alanine and valine) at the P'1 position. As shown in Table 1 of the Specification, OmpT D97H (1) cleaves PRA at an efficiency of 8.4% and (2) PRV at an efficiency of 7.8%. Both efficiencies are greater than the wild-type OmpT (D98D) and OmpT D97E variant (Asp 97 is substituted by glutamic acid). It is also unexpected that OmpT D97H variant is able to cleave substrates having isoleucine (I), methionine (M), threonine (T), or asparagine (N) at the P'1 position. *See* Table 1 of the Specification (showing that no other OmpT variant is capable of cleaving PRI, PRM, PRT, or PRN).

Given at least these arguments, claim 49 as amended is nonobvious over cited references. Dependent claim 51 is likewise nonobvious for at least the same reasons. Applicants respectfully request withdrawal of the rejection and allowance of claims.

11.6. Claims 49

The Office rejects claims 49 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of **Okuno 2002a**, **Dekker**, and **Kramer**, in view of **Metzler**. Office Action, page 43. The rejection appears to be a duplicate of the rejection set forth and discussed in Section 11.5 *supra*. Applicants traverse the rejection as discussed in Section 11.5 *supra*. Applicants respectfully request withdrawal of the rejection and allowance of claims.

CONCLUSION

In view of the above arguments and amendments to the claims, Applicant submits that the claims are in condition for allowance and respectfully request reconsideration and timely allowance of the claims.

Should the Office have any questions or comments regarding Applicant's amendments or response, please contact Applicant's undersigned representative at (202) 230-5119. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number. If an Appeal fee is required to maintain pendency of the present application, the Office is authorized to charge the Appeal fee to the deposit account above and use this paper as a constructive Notice of Appeal.

Respectfully Submitted,

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Exhibit I

Abbreviations Used for Cited References

Dekker *et al.*, 40 BIOCHEMISTRY 1694 (2001) ("Dekker")

Kramer *et al.*, 505 FEBS LETTERS 426 (2001) ("Kramer")

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Okuno *et al.*, 66 BIOSCI. BIOTECHNOL. BIOCHEM. 127 (2002) ("Okuno 2002a")

Okuno *et al.*, 36 BIOTECHNOL. APPL. BIOCHEM. 77 (2002) ("Okuno 2002b")

Stumpe *et al.*, 180 J. BACTERIOL. 4002 (1998) ("Stumpe")

Sugimura *et al.*, 170 J. BACTERIOL. 3650 (1988) ("Sugimura 1988a")

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U.S. Patent No. 5,506,120 ("Yamamoto")